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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HORNING, MICHELLE S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,087	BACHMANN ET AL.	
	Examiner	Art Unit	
	Michelle Horning	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/17/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *9-10, 29-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-28,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to communication filed on 5/17/2006. The current status of the claims is as follows: claims 1-8, 11-28 and 50-51 are under examination and claims 29-49 have been withdrawn. Claims 9-10 are drawn to non-elected species.

IDS

The Information Disclosure Statement filed November 17, 2003 has not been fully considered. This submission cites more than 500 documents requiring a listing on an PTO-1449 of nearly 130 pages. In an initial review of 21 U.S. patents and published applications, the Office finds that only 2 of these documents are material to patentability of one or more claims in accordance with 37 CFR 1.56. A review of the first 21 publications revealed only 5 deemed to be material to patentability. In view of the very low percentage of references material to patentability in the sampled documents reviewed, the submission is not in compliance with 37 CFR 1.56 and 1.98. Accordingly, the remaining references will not be considered.

Claim Rejections

35 U.S.C. 112, 2nd paragraph35 U.S.C. 101

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 provides for the use of a composition for the manufacture of a medicament, but, since the claim does not set forth any steps involved in the

method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. 101

Claim 51 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Of note, claim 51 is interpreted as a product claim with an intended use as indicated by the Requirement for Restriction.

35 U.S.C. 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for inducing anti-Abeta 1-6 antibodies capable of binding to amyloid plaques (page 9, 23 paragraph), does not reasonably provide enablement for a medicament. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

State of the prior art. The prior art reference, Schenk et al (1999, cited), show that immunization with amyloid beta peptide (1-42) greatly reduces the development of the AD-like pathology, such as reduction in plaque formation, that otherwise occurs in PDAPP mice. However, no prior art suggests that this finding resulting from an animal model could translate into successful treatment of Alzheimer's disease in humans. In fact, Holtzman et al (2002) disclosed that phase II trial of active immunization by Elan Pharmaceuticals with amyloid beta (1-42) in humans led to the occurrence of CNS inflammation and, as a consequence, the trials were halted. Further, the cause of the inflammation was not known at the time of the invention.

Guidance in the specification. The specification fails to provide adequate guidance for the intended use as a medicament.

Predictability of the art. Holtzman et al suggest that the success of possible future studies of immunization would not be likely without the further evaluation of questions. Some of the questions include whether active immunization be accomplished without side effects, will treatment result in rapid and/or long term changes in cognition

in patients with AD and will immunization prevent or delay the onset of dementia? Further, Holtzman et al suggests that there are many questions, more than suggested, that "will need to be addressed over the next decade in determining whether active immunization with Aβ will be of use in human AD (Alzheimer's disease).

Working examples. No working example is disclosed in the specification for the specific use of medicaments.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to compositions which form an ordered and repetitive antigen array. Within these claims, the compositions are described as comprising lysine modifications via removal, insertion, addition by way of substitution and deletion.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical

> and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed or through disclosure of a functional characteristic of the claimed genus coupled with a known or disclosed non-functional characteristic (structure) that correlates to the function.

In the present application, the specification fails to identify the specific region within the protein that is required in the formation of a molecular antigen array. Thus, without any relationship of structure to function in the peptide, it is not known to one of ordinary skill in the art where peptide modification(s) (including lysine deletion, substitution and insertion) and how many of these modifications can occur so that the ordered arrangement found in the antigen array is maintained. Further, the specification does not disclose the substituting residue in place of a native lysine so that the peptide can maintain stability and conformation.

In contrast to the teachings of the application, the art teaches that, although proteins tend to permit some level of amino acid substitution, the results of any specific such modification are generally unpredictable in the absence of specific guidance as to

the relationship between a targeted residue and the function and structure of the protein. See e.g., Bowie et al (1990). Thus, the art provides uncertainty regarding the operability of modified peptides encompassed by the claims to induce the desired ordered and repetitive array. In addition, the application provides little, if any, guidance as to what modifications can be made to the peptides as to retain the ability to form the ordered and repetitive arrays. For these reasons, and as the application provides no operable species of the claim genera, much less a representative number, there is insufficient descriptive support in the application to demonstrate possession of the claimed genera of methods, involving the use of modified peptides to form an ordered and repetitive array.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for species a, b and therefore, identical sequences c, d, f and g, does not reasonably provide enablement for e, SEQ ID NO:86. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)).

Guidance in the specification. The specification provides little guidance regarding which residues are necessary to induce a specific immune response against Abeta 1-6.

Of the six residues, SEQ ID NO:86 contains a serine residue while others contain an alanine residue at the corresponding site. Secondly, SEQ ID NO:86 contains a tyrosine residue in place of a phenylalanine found in the other peptides. The specification fails to address these differential residues.

Predictability of the art. Because the specification fails to adequately describe the SEQ ID NO:86 (eg by way of working examples), it is uncertain as to what results the composition would generate. Further, the art teaches that, although proteins tend to permit some level of amino acid substitution, the results of any specific such modification are generally unpredictable in the absence of specific guidance as to the relationship between a targeted residue and the function and structure of the protein. See e.g., Bowie et al (1990).

Working examples. No working example is disclosed in the specification for SEQ ID NO:86 containing compositions.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

35 U.S.C. 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 19-23 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sebbel et al (US Patent No.: 6,964,769) in view of Frenkel et al (PNAS, 2000). Sebbel et al teach compositions for vaccines that form ordered and repetitive antigen or antigenic determinant arrays (entire document). Sebbel et al specifically disclose a composition comprising a) core particle and b) an antigen or antigenic determinant. Further, the antigen or antigenic determinant has at least one 2nd attachment site selected from i) an attachment site not naturally occurring with said antigen or antigenic determinant and ii) an attachment site naturally occurring with said antigen or antigenic determinant. As disclosed by Sebbel et al, an ordered and repetitive antigen array is formed by the core particle and antigen or antigenic determinant via association of the 2nd attachment site to the 1st attachment site of the core particle (entire document). Sebbel et al disclose that the association of the 1st and 2nd attachment sites may occur through fusion (col. 17, 1st paragraph), covalent or non-peptide bonds (col. 31, 2nd paragraph). To link an antigen to a scaffold, Sebbel et al teach substitution, deletion (col. 24, lines 51-55) and insertion of lysine residues (Example 23). As taught by Sebbel et al (col. 6, lines 20-31), the core particle is

selected from the group consisting of: a virus, bacterial pilus, bacterial pilin, bacteriophage, a VLP or viral capsid. Moreover, it is disclosed that the core particle may be a recombinant protein selected from the group: Rotavirus, Norwalk virus, Alphavirus, Foot and Mouth Disease virus, Retrovirus, Hepatitis B virus, Tobacco mosaic virus, Flock House Virus, human Papilomavirus (col. 6, lines 29-37) and recombinant phages (col. 12, line 21). Sebbel et al further discloses an embodiment in which the core particle comprises, or alternatively consists of, one or more different Hepatitis core proteins (col. 5, lines 38-40).

Although Sebbel et al disclose the use of amyloid beta peptide (1-42) or a fragment thereof as an antigen for therapeutic action against Alzheimer's disease (col. 35, lines 35-58), they do not disclose the use of amyloid beta peptide (1-6) in particular. Frenkel et al, however, disclose immunization against amyloid beta peptide via amyloid beta peptide (1-6) with phage and antibodies resulting from peptides bearing the EFRH motif, including amyloid beta peptide (1-6), inhibited aggregation (see Immune Specificity of the EFRH Phage Anti-Sera Toward Whole AbetaP, Results, page 11457 and Discussion).

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Sebbel et al and Frenkel et al to enhance immune responses. One would have been motivated to do so, given the suggestion by Frenkel et al that the antibodies resulting from the immunization are similar in their anti-aggregating properties to antibodies raised by direct injection with fibrillar toxic beta-amyloid. Such antibodies are able to sequester the peripheral beta-amyloid, thus avoiding the passage

through the blood-brain barrier and to dissolve already formed beta-amyloid plaques (see Discussion, page 11458). There would have been reasonable expectation of success in immunized animals given that Frenkel et al demonstrate a production of high titer of antibodies with high binding specificity in a short period of time without the use of adjuvants, the self-expression of the antigen leads to long-lasting immunization and this method leads to anti-aggregating antibodies which recognize whole beta-amyloid peptide (see Discussion).

Claims 4, 6-8,11 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sebbel et al and Frenkel et al as applied to claims 1-5, 19-23 and 50 above, and further in view of Vasiljeva et al 1998. Sebel et al and Frenkel et teach the use of phage conjugates, however, neither reference specifically discloses the use of Q beta phage, a phage whose use is well known in the prior art. Vasiljeva et al overcome this deficiency by disclosing a method in which recombinant Q beta coats provide "ensured specific antigenicity and immunogenicity" as demonstrated by a model insertion (see Abstract). Thus, this invention would have been obvious to one skilled in the art at the time the invention was made.

Claims 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sebbel et al, Frenkel et al and Vasiljeva et al as applied to claims 1-8, 11-23 and 50 above, and further in view of Robinson and Sauer (1998). Sebbel et al teach the use of short peptide linkers to link the antigen or antigenic determinant to the scaffold (Example 6). Many prior art references disclose that the –SH group of a cysteine residue is a reactive moiety which may then lead to crosslinking of a scaffold to

an antigen or antigenic determinant, including Sebbel et al (col. 33, lines 62-67 through col. 34, lines 1-22). It is further known in the prior art that glycine is a residue that commonly serves in peptide linkers and one would have been motivated to use glycine residues in designed linkers because "the absence of a β-carbon permits the polypeptide backbone to access dihedral angles that are energetically forbidden for other amino acids" (Robinson and Sauer, see Disscussion). Thus, the use of designed linkers consisting of cysteine and glycine residues would have been obvious to one skilled in the art at the time the invention was made.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sebbel et al, Frenkel et al and Vasiljeva et al as applied to all claims above, and further in view of Golmohammadi et al (1996). Golmohammadi et al disclose SEQ ID NO:4, a bacteriophage Q beta capsid of which the structure was solved. The protein structure reveals the many contacts at the dimer interface between two subunits, including disulphide and salt bridges mediated by cysteine and lysine residues. Because the solved structure of the coat protein (SEQ ID NO:4) can be used a guide in mutagenesis to lead to the formation of an organized and repetitive antigen or antigenic determinant array on the surface of the scaffold, one would have been motivated to use a peptide whose structure has been solved or SEQ ID NO:4. Thus, this invention would have been obvious to one skilled in the art at the time the invention was made.

CONCLUSION

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michelle Horning whose telephone number is 571-272-9036. The examiner can normally be reached on Monday-Friday, 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 570-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for unpublished application is available through Private PAIR only. For more information about PAIR system, see htt://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michelle Horning
Patent Examiner

JEFFREY S. PARKIN, PH.D.
PRIMARY EXAMINER